CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019651/S005

PHARMACOLOGY REVIEW(S)

Pages: 101 through 125

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summary of all Mistomorphologic Findings

						INC.	INCIDENCE OF OBSERVATION (NUMERIC)	F OBSER	VAT10N	ERVATION (NUMERIC)	9			-
	•	•			MALES	ES.		•			FEMALES	ES		:
	OBSERVATIONS	TREATHENT	0 mg/kg	0 200 mg/kg mg/kg	1000 2000 mg/kg mg/kg	2000 mg/kg			PO Pmg/kg	200 mg/kg	200 1000 2000 mg/kg mg/kg mg/kg	2000 mg/kg		
	MUSCULOSKELETAL SYSTEM:-											:	:	:
	BONE:		(90)	(20)	(20)	(20)		~ ~	(20)	(\$0)	(20)	(20)		
	Solitery cyst(s)					-		* *						
	CHONDROSARCONA [H]							• •			_			
	Callus			-				* *						
	JOINT(S):		(20)	(48)	(20)	(20)			(48)	373	33	(67)		
	No abnormality detected		2	17	¥	<u>\$</u>	-	* *	~	2	2	%		
	Metastatic aite: HISTIOCYTIC SARCOMA [N]	ICONA (N)						* *	_			-		
	Focal/multifocal acute/chronic inflammation		•	-				* * *	_		-	-	·	
	Focal/multifocal vasculitis		_	-		· <u> </u>		* * *	-	_	-	-		·
	Arthropathy		38	22	ž	8		• • •	12	x	22	- -		
	Suppurative arthritis			***************************************				• • •	-					
- :		-	-		-	-	-	•	-	-	-	-	_	_

Figures in brackets represent the number of animals from which this tissue was examined microscopically. The absence of a numeral indicates that the lesion specified was not identified

Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summery of all Mistomorphologic Findings

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					INCI	INCIDENCE OF OBSERVATION (NUMERIC)	OBSERVAL	¥ .	MERIC	_			
•				MALES	£		*			FEMALES	ES		:
OBSERVAT I ONS		0 mg/kg	200 mg/kg	1000 mg/kg	1000 2000 mg/kg mg/kg		#O #mg/kg	kg 200	200 10 mg/kg mg	9/48	1000 2000 mg/kg mg/kg		:
MUSCULOSKELETAL SYSTEM:	•			•	:			:	:	:			:
JOINT(S):	- "	(50)	(84)	(20)	(20)		± ••	(48)	<u> </u>	32	(65)		
focal vascular mineralization			-				* *				,	· <u>·</u>	
LYMPHONA (M)	-	~	_	-	-		* *	_		_			
focal articular cartilage degeneration	ration		-				~ ~						
focal/multifocal capsular cyat(s)	2			-	-		• •						
focal/multifocal/diffuse synovial inflammation/hyperplasia/congestion	_ <u>\$</u>	~	m	-			.			~	-		
SKELETAL MUSCLE:		(20)	(64)	(20)	(20)		خ ته ه	(49)	(20)	(50)	(20)	-	
No abnormality detected		%	33	3	33		90 100 100 100 100 100 100 100 100 100 1		-	37	0,	<u> </u>	
Metastatic site: HISTIOCYTIC SARCONA [M]	COMA (M)		~		-		-		·	-		-	
Focal/multifocal acute/chronic inflammation		~	4	•	-		m = == ==	<u> </u>		•	~		

Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summary of all Nistomorphologic findings

•

OBSERVATIONS TR	TREATMENT												:
				MALES	ES		•			FEMALES		· · · · · · · · · · · · · · · · · · ·	
MUSCULOSKELÈTAL SYSTEM;-)/kg	200 mg/kg	200 1000 2000 mg/kg mg/kg	2000 mg/kg		7/6mm	200	#0 200 1000 2000 ##9/kg mg/kg mg/kg	20 E	000 1/kg	<u></u>	
			:		:	:		:	:	:	:	<u>: </u>	
SKELETAL MUSCLE:		(20)	(65)	(20)	(S ₀		(67) #		(50)	(20)	(20)		
focal vascuiitis		_			~		• •	_		·			
LYMPHOMA (M)	<u> </u>	~	~	-	7		~	<u> </u>	-		~		
focal/NOS hematoma	<u></u>			-			* *					<u> </u>	
focal/multifocal myofiber degeneration		~	•	•	•		m ** ** *		<u> </u>			··· ··	
Autolysis			m	-	-		-	~				·	
focal/multifocal myofiber atrophy		_		-			• •		-		~		
NERVOUS SYSTEM:-							* *						
DRAIN:		(20)	(30)	(20)	(20)		(20)	(30)		(20)	(20)		
No abnormality detected	-	31	×	53	5		20 20 20 20 20 20 20 20 20 20 20 20 20 2	77	33				
Metastatic site: MISTIOCYTIC SARCOMA [M]	E		-				-					· · · -	

Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Nonths) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7

Summary of all Mistomorphologic Findings

)H	IDENCE	INCIDENCE OF OBSERVATION (NUMERIC)	VATION	SERVATION (NUMERIC)	<u></u>			
				MALES	ES					FEMALES	LES		
OBSERVATIONS	TREATMENT O	O Mg/kg	200 mg/kg	0 200 1000 2000 mg/kg mg/kg mg/kg mg/kg	2000 mg/kg			10 mg/kg	200 mg/kg	#0 200 1000 2000 #mg/kg mg/kg mg/kg	2000 mg/kg		
MERVOUS SYSTEM:-	8 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9			:	:					:			
BRAIN:		(20)	(\$0)	(20)	(30)			(\$0)	(20)	(50)	(30)		
Metastatic site: GRANULOCYTIC LEUKENIA (N)	EUKENIA		-		,								
Focal/multifocal acute/aubacute		-	~							~	•		
focal/multifocal vasculitis		m	-					-		-			
Multifocal axonal awelling								-					
Multifocal/NOS spongiosis				-				~	4	•			
focal/multifocal mineralization		2	2	~	7			m	4	۰	m		
LYMPHOMA (M)		m	_	_	_			~		m	-	•	
focal perivascular lymphoid infiltration	Ittration				-		k *						
Focal hemorrhage								-					
							ŀ						

figures in brackets represent the number of animals from which this tissue was examined microscopically. The absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summery of all Mistomorphologic Findings

MALES MALE						:	INCIDENCE OF OBSERVATION (NUMERIC)	MSERVATIO	N (NUMERIC)	110		:	
TREATMENT 0 200 1000 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 60 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000 2000					PAL	so L		***		FEMA	LES		:
1 1 1 1 1 1 1 1 1 1	,	TREATMENT		200 mg/kg	1000 mg/kg	2000 mg/kg		#0 ##9/kg	200 mg/kg	1000 mg/kg	2000 mg/kg		
1 1 1 1 1 1 1 1 1 1	NERVOUS SYSTEM:-	•		:	:		:		<u>:</u>		:	:	:
1 1 1 1 1 1 1 1 1 1	BRAIN:		(50)	(20)	(50)			# (\$0)			(50)		
1 1 1 1 1 1 1 1 1 1	Focal gliosis	-		-				-		_			-
1 1 1 1 1 1 1 1 1 1	Multifocal neuronal atrophy							• •		-			
30 36 34 38 6 7 31 33 31 33 EUKENIA 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	SCIATIC NERVE:		35	(45)	32	(48)		(35) #	_	(99)	(95)		
EUKENIA 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	No abnormality detected		2	28	×	8	-			H	39		
EUKENIA 1 3 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Metastatic aite: MISTIOCYTIC SAR	CONA (M)		-			- ,	-	-		-		
~ - ~	Metastatic site: GRANULOCYTIC LE	EUKENIA				_		* * *					
Focat/multifocal mineralization 1 1 1 1 2 2 3 2	focal/multifocal perineural/NOS aubacute inflammation				m			~		~			
LYMPHONA (M) 1 1 1 1 2 2 3 2	Focal/multifocal mineralization			···	_	·							
	LYMPHONA (N)		-	-	-	-	<u></u>	~		m	~		

figures in brackets represent the number of animals from which this tissue was examined microscopically. The absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summary of all Mistomorphologic Findings

					INCI	INCIDENCE OF OBSERVATION (NUMERIC)	JOSERVAT IC	M (NUMER	NUMERIC)		
				MALES	23				FEMALES	ILES	
OBSERVATIONS	TREATMENT	mg/kg	200 mg/kg	1000 mg/kg	1000 2000 mg/kg mg/kg		PO Pmg/kg	200 mg/kg	1000 mg/kg	1000 2000 mg/kg mg/kg	
						:	•	-			
MERVOUS SYSTEM:-							. • •				
SCIATIC WERVE:		(47)	(45)	(47)	(48)		()	3	(46)	(95)	
Multifocal/segmental demyelination	tion	16	1	2	•		~	12	2	~	
SPINAL CORD:		(20)	(20)	(\$0)	(20)		(20)	(49)	(50)	(50)	-
No abnormality detected		2	ž	3	&		33		3	32	
Metastatic site: NISTIOCYTIC SA	OCYTIC SARCONA [M]		~		-		-	_	~	-	
focal/multifocal acute inflammation	tion		-				* *			~	
focal/multifocal vasculitis		-	-				-	-	_	-	
Focal/multifocal axonal swelling	•	11	2	•	5		*	2	2	2	
Multifocal spongiosis							* * :	n	-		
Multifocal malacia			-								
LYMPHOMA (M)		m	_	-	~		8	-	-	-	

Figures in brackets represent the number of animals from which this tissue was examined microscopically to The absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summary of all Mistomorphologic Findings

OBSERVATIONS TREATMENT O mg/kg MERVOUS SYSTEM: SPINAL CORD: focal/multifocal lymphold infiltration focal/multifocal hemorrhage Multifocal cystic dilation focal/multifocal neuronal/axonal focal/multifocal neuronal/axonal focal/multifocal neuronal/axonal focal/multifocal neuronal/axonal focal/multifocal neuronal/axonal focal/multifocal neuronal/axonal	200 mg/kg	MAIFS								
INFILTER ION wonel yet(6)	200 mg/kg		ES		•		FEMALES	168		
infiltration konal		1000 2000 mg/kg mg/kg	2000 mg/kg		#0 #mg/kg	#0 200 1000 2000 ##\$/kg mg/kg mg/kg	1000 mg/kg	2000 mg/kg		<u> </u>
infiltration incomplete in incomplete in inc			:	:				:	:	•
focal/multifocal tymphoid infiltration focal/multifocal hemorrhage Multifocal cystic dilation focal/multifocal neuronal/axonal degeneration focal squamous epithelial cyst(s) Autolysis	(30)	(\$0)	(30)		((20)	(67)	(\$0)	(\$0)		
focal/multifocal hemorrhage Multifocal cystic dilation focal/multifocal neuronal/axonal degeneration focal squamous epithelial cyst(s) Autolysis					-		-	-		
Multifocal cystic dilation Focal/multifocal neuronal/axonal degeneration Focal squamous epithelial cyst(s) Autolysis	_	-			~ ~					
focal/multifocal neuronal/axonal degeneration focal squamous epithelial cyst(s) Autolysis					• •					
Focal squamous epithelial cyst(s) Autolysis			_	 :	***		~			
Autolysis	-				• •					
	_				• •	-				
REPRODUCTIVE STRIET - PERMIE:					• •					
OVARY(IES):					(48) #	(47)	(20)	(48)		
No abnormality detected					-	~	4	\$		
Metastatic site: HISTIOCYTIC SARCONA [M]						~	~	~		

Figures in brackets represent the number of animals from which this tissue was examined microscopitally the lesion specified was not identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Surmary of all Mistomorphologic Findings

					- DAC	INCIDENCE OF OBSERVATION (NUMERIC)	OBSERVAT	2	UMERIC				
				MALES	ES		•			FEMALES	ES		:
OBSERVATIONS	TREATMENT	0 mg/kg	200 mg/kg	1000 mg/kg	1000 2000 mg/kg mg/kg		#0 #m9/kg		200 1000 2000 mg/kg mg/kg	000 9/kg	2000 mg/kg		
REPRODUCTIVE SYSTEM - FEMALE:-			:	:	:	:		<u>:</u> :	:		:		
OVARY(1ES):						·	<u>.</u>	— (97)	- 23	(36)	(4)		
GRANULOSA-THECA CELL TUMOR (M)							-		_		}		
Focal/multifocal periovarian/NOS acute/chronic inflammation	. 60					·	* * *		. 2	5	5		
Muttifocal vasculitis							-					-	
One examined													
Multifocal thrombosis							-						
TERATONA (8)				**			-					-	
Multifocal/diffuse ceroid/NOS pigmentation		· · · · · ·					***					·	
MYXOMA [8]							* *						
Focal/muttifocal mineralization							* *			~			
		_	_	_	_	_	•		-	_	_	_	

Figures in brackets represent the number of animals from which this tissue was examined microscopically.

The absence of a numeral indicates that the tesion specified was not identified

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Oncogenicity Study (24-Nonths) of 5-ASA in the Diet of Swiss Mice Project No. B62.09.00-CD Pathology Table 7

Summery of all Mistemorphologic Findings

2000 mg/kg **(48**) 200 1000 mg/kg mg/kg (20) INCIDENCE OF OBSERVATION (NUMERIC) (47) Pmg/kg (48) 200 1000 2000 mg/kg mg/kg 0 mg/kg TREATMENT Multifocal/diffuse stromal/stromal-cell hyperplasia Multifocal/diffuse granulosa-cell Focal lymphoid infiltration REPRODUCTIVE SYSTEM - FEMALE: LEICHYOSARCOMA [M] **COSERVATIONS** LYMPHOMA (M) LUTEONA (B)

OVARY (IES):

figures in brackets represent the number of animals from which this tissue was examined microscopically. The absence of a numeral indicates that the lesion specified was not identified

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Focal/multifocal/diffuse epithelial/tubular/papillary hyperplasis

hyperplasia

Multifocal hyalinization

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summary of all Mistomorphologic findings

					INC	INCIDENCE OF OBSERVATION (NUMERIC)	DBSERV	101	NUMER	a			
•				MALES	£5		-			FEMALES	83		
OB SERVATIONS	TREATMENT	0 mg/kg	0 200 1000 2000 mg/kg mg/kg mg/kg	1000 mg/kg	2000 mg/kg		2 .	#0 2 ##9/kg ==	00 9/kg	200 1000 2000 mg/kg mg/kg mg/kg	2000 mg/kg		
REPRODUCTIVE SYSTEM - FEMALE:-						<u>: </u>	•	:	:		:		
OVARY(1ES):							* *	(48)	(47)	(20)	(64)		
Focat/multifocat/NOS hemorrhage/hematoma							* * *	•	•	~	~		
Mass (1): HEMANGIOSARCONA (N)	-						* *		•	_			
Multifocal fibrosis							* * :						
focal/multifocal/NOS cyst(s)							* * :	33	8	75	35		
CHOR LOCARCONONA [H]	_					**			•				
Autolysis							• •		~	-			
Diffuse/NOS atrophy			-				• •	_	٠,				
Multifocal angiectasis							• •		_	_	•		
Focal/multifocal/diffuse amyloidosis	doste					•	h 44 1	=	•	٥	•		
Tubular/NOS ADENONA [8]							* ,**		_	_	-	•	

Figures in brackets represent the number of animals from which this tissue was examined microscopically. The absence of a numeral indicates that the lesion specified was not identified

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> Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summary of all Mistomorphologic findings

					INCIDEN	INCIDENCE OF OBSERVATION (NUMERIC)	ERVATION	CNUMER	10			:-
				MALES	v		**		FEMALES	LES		:
OG SERVATIONS	TREATMENT	0 mg/kg	200 mg/kg	0 200 1000 2000 mg/kg mg/kg mg/kg mg/kg	2000 mg/kg		#O #mg/kg	60 200 1000 2000 6mg/kg mg/kg mg/kg	1000 mg/kg	2000 mg/kg		:
REPRODUCTIVE SYSTEM - FEMALE:-		•	:		:	:				:	<u>:</u> :	:
UTERUS:							(20)	(50)	(\$0)	(20)	,	
No abnormality detected							·	۰	m	7		
Metastatic site: MISTIOCYTIC SARCONA [M]	ARCONA (N)						`	~	~	-	<u></u>	
Primary site: HISTIOCYTIC SARCONA (M)	DHA (M)				· .		m e e:	m	~	m		
Multifocal/diffuse/NOS Cystic Endometrial Hyperplasia	-						% * * *	8	39	38		
Primary site: STROMAL SARCOMA [M]							• •		-			
Focal endometrial stromal polyp(s)	(*)						-		-	-		
focal/multifocal vasculitis							.	m	7	~		
focal/multifocal adenomyosis								~		~		
Multifocal hemosiderin pigmentation	tion		_							-		
Focal endometrial necrosis				•								
	_	-	_	_ ;		_	_		_		_	-

figures in brackets represent the number of animals from which this tissue was examined microscopically the absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pethology Table 7 Summary of all Mistomorphologic findings

					JWC .	IDENCE	0f 08SE	RVATION	INCIDENCE OF OBSERVATION (NUMERIC)	10)		•	:
				MALES	ES .					FEMALES		:	:
OBSERVATIONS	TREATMENT	0 mg/kg	200 mg/kg	0 200 1000 2000 mg/kg mg/kg	2000 mg/kg			PO Pmg/kg	#0 200 1000 2000 mg/kg mg/kg mg/kg	1000 mg/kg	2000 mg/kg		:
REPRODUCTIVE SYSTEM . FEMALE:-					:								<u>.</u>
UTEAUS:								(20)	(8)	(6)	1037		
Multifocal mineralization										3	600		
LYMPHONA [M]								^		·	•		
Multifocal myometrial lymphanglectasis	ectesis							-			•		
LEIONYOSARCONA (M):									-	-			
LEICHYCHA (B)			_						•	-			
focal/multifocal/diffuse endometrial/glandular/luminal/NOS acute/chronic/chronic-active inflammation	S O					<u></u>		•	٠	•	•0		
focal stromal cell hyperplasia								-		_			
Multifocal cervical glandular hyperplasia							~ ~ .			_			

Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summary of all Mistomorphologic Findings

Mg/kg mg/kg mg/kg mg/kg (\$0) (20) INCIDENCE OF OBSERVATION (NUMERIC) (20 (20) 200 | 1000 | 2000 mg/kg MALES mg/kg TREATHENT focal/multifocal hematoma/endometrial focal/multifocal glandular dilation endometrial/myometrial angiectasis Focal endometrial/NOS cyst(s) focal/multifocal amyloidosis REPRODUCTIVE SYSTEM - FEMALE: focal/multifocal/diffuse HEMANGIOSARCONA (M) Diffuse congestion tuminel diletion **CBSERVATIONS** hemorrhage Autolysis UTERUS:

figures in brackets represent the number of animals from which this tissue was examined microscopically. The absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summary of all Mistomorphologic findings

					INCIDE	INCIDENCE OF OBSERVATION (NUMERIC)	DBSERVA	8	NUMERS	5			
•				MALES	ES		-			FEMALES	LES		:
OB SERVATIONS	TREATMENT	0 mg/kg mg/kg	200 mg/kg	1000 mg/kg	1000 2000 mg/kg mg/kg		2	70 70 70 70 70 70	90 kg	200 1000 2000 mg/kg mg/kg mg/kg	2000 mg/kg		
REPRODUCTIVE SYSTEM - FEMALE:-					:			:			:	:	
UTERUS:							* *	(50)	(20)	(50)	(20)		
ADENOCARCINOMA (M)							* *				_		
Focal myometrial abscess(es)							* *	_					
VAGINA:							ن * *	(35)	(43)	(95)	(95)		
No abnormality detected							* *	- 51	13	*	22		
Primery site: HISTIOCYTIC SARCOMA [H]	FA (N)											<u>-</u> .	
Metastatic site: HISTIOCYTIC SARCOMA [M]	RCOMA (N)						* *	~	-	-	-		
Metastatic site: STROMAL SARCOMA [M]	- CE 4						* *			-			
Focal/multifocal chronic inflammation	metfon						* *	~	•	•	2		
Focal/multifocal vasculitis							* *		2	2			
Focal/multifocal/diffuse/NOS mucoid	pioo		*			<u> </u>			=	~	•		

Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Nonths) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summary of all Mistomorphologic Findings

OBSERVATIONS REPRODUCTIVE SYSTEM - FEMALE: VAGINA: LYMPHONA (M) Multifocal inflammation Luminal neutrophilic infiltration Focal/multifocal epithelial hyperplasia Multifocal fibrosia Focal/multifocal cyatic/NOS glandular Gongeation Congeation	INCIDENCE OF OBSERVATION (NUMERIC)	(NUMERIC)	
RVATIONS RVATIONS CIIVE SYSTEM - FEMALE:- Sfocal inflammation /multifocal epithelial hyperplasia focal fibrosis /multifocal cystic/HOS glandular fon stion	MALES	FEMALES	
MEPRODUCTIVE SYSTEM - FEMALE:- VAGINA: LYMPHOMA (M) Multifocal inflammation Luminal neutrophilic infiltration Focal/multifocal epithelial hyperplasia Multifocal fibrosis Focal/multifocal cystic/NOS glandular Gongestion Congestion		#0 200 1000 2000 #mg/kg mg/kg mg/kg	
VAGINA: LYMPHONA [M] Multifocal inflammation Luminal neutrophilic infiltration Focal/multifocal epithalial hyperplasia Multifocal fibrosis Focal/multifocal cystic/NOS glandular dilation Congestion			:
LYMPHOMA (M) Multifocal inflammation Luminal neutrophilic infiltration Focal/multifocal epithelial hyperplasia Multifocal fibrosis Focal/multifocal cystic/MOS glandular dilation Congestion	(33)	(97) (97) (87)	
Multifocal inflammation Liminal neutrophilic infiltration Focal/multifocal epithelial hyperplasia Multifocal fibrosis Focal/multifocal cystic/NOS glandular dilation Congestion		,	
tuminal neutrophilic infiltration Focal/multifocal epithelial hyperplasia Multifocal fibrosis Focal/multifocal cystic/NOS glandular ditation Congestion Autolysis			
Focal/multifocal epithelial hyperplasia Multifocal fibrosis Focal/multifocal cystic/NOS glandular dilation Congestion Autolysis			
Multifocal fibrosis Focal/multifocal cystic/NOS glandular dilation Congestion			
Focal/multifocal cystic/NOS glandular ditation Congestion Autolysis			
Congestion	~	2 2	
Autolysis		-	· .
	n	2	
ADENOMA (9)	* *	-	

figures in brackets represent the number of animals from which this tissue was examined microscopically. The absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summary of all Mistomorphologic findings

					INCIO	INCIDENCE OF OBSERVATION (NUMERIC)	OBSER	DSERVATION (NUMERIC)	CHUMER	3			
				MALES	S.					FEMALES	LES	:	
OBSERVATIONS	TREATMENT	0 mg/kg	200 mg/kg	1000 2000 mg/kg mg/kg	2000 mg/kg			70 mg/kg	200 mg/kg	200 1000 2000 mg/kg mg/kg	2000 mg/kg	:	
REPRODUCTIVE SYSTEM - MALE:-					:			:			:	:	
EPIDIDYMIS(DES):		(99)	(20)	(65)	(\$0)	••	•						
No abnormality detected		22	20	\$	5								
Metastatic site: HISTIOCYTIC SARCOMA [M]	ARCOMA [H]		m		-							••	
Metastatic site: GRANULOCYTIC LEUKEMIA [M]	LEUKENIA		-			<u>. </u>							
Aspermia		•	m	4	~	-	* **						
Focal/multifocal/diffuse capsular/NOS subscute/chronic inflammation	ler/HO\$	5	6	12	2					···-			
Multifocal peri-epididymal acuta inflammation	2		8			• • • • • • • • • • • • • • • • • • • •							
Focal/multifocal vasculitis		-	-		-		. ~ *						
One examined		-	m	\$	-				•				
focal sperm granuloma(ta)					_				•				

figures in brackets represent the number of animals from which this tissue was examined microscopically the absence of a numeral indicates that the lesion specified was not identified

22-fEB-96 72 PLACES VB.200

Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summery of all Mistomorphologic Findings

		:				DENCE OF	INCIDENCE OF DESERVATION (NUMERIC)	RVATION (NUMERIC)	ERIC)		
				MALES	ES		•		FEM	FEMALES	
OBSERVATIONS	TREATMENT	0 mg/ke	200 mg/kg	200 1000 2000 mg/kg mg/kg mg/kg	2000 mg/kg	• • • • • • • • • • • • • • • • • • •	2	60 200 1000 2000 6mg/kg mg/kg mg/kg	1000 mg/kg	2000 mg/kg	
REPRODUCTIVE SYSTEM - MALE:-				<u> </u>		:					
EPIDIDYMIS(DES):		(50)	(20)	(65)	(\$0)		* *				
Multifocal tuminal cellular aggregate(a)	regate(a)	-					••				
Multifocal epithelial vacuolation	8	~					* *	-			
Diffuse/NOS oligospermia		2	21	۰	•		* *				
Focal/multifocal interatitial/wascular/NOS mineralization		-	-	~	•	<u> </u>	* * * *				
Primary site: MESOTHELIGHA [N]		_					••				
LYMPHOMA (M)		.~	~		~		* *		-		
Multifocal interstitial fibrosis		-	~	-		-	* *				
focal/multifocal ductular dilation	8	,	•	~	•		• •				
Autolysis			~	~		· <u> </u>	* *				

Figures in brackets represent the number of animals from which this tissue was examined microscopically the absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summary of all Mistomorphologic Findings

		_	:			INCIDENCE OF OBSERVATION (NUMERIC)	OBSERV	ATTON	(MUMER!	3			
•	•			MALES	S.		*			FEMALES	ES		:
OBSERVATIONS		0 mg/kg	0 200 1000 2000 mg/kg mg/kg mg/kg	1000 mg/kg	2000 mg/kg		2 .	1/kg	200 mg/kg	200 1000 2000 mg/kg mg/kg mg/kg	2000 mg/kg		<u> </u>
REPRODUCTIVE SYSTEM - MALE:-	•	•				:	•	:			:	:	
EPIDIDYMIS(DES):		(99)	(20)	(65)	(\$0)		* * *						
Multifocal interstitial amyloidosis	losts			~	~		• •						
PROSTATE:		(30)	(20)	(20)	(65)		* * '					-	
No abnormality detected		٥	۰	Ξ	75		* * *						
Metastatic site: HISTIOCYTIC SARCONA [M]	RCOMA (M)		4		~		* * 1						
Metastatic site: GRANULOCYTIC LEUKEMIA (M)	EUKENIA		-				k % *2 (···			
Focal/multifocal/diffuse interstitial/NOS acute/subscute/chronic inflammation	/chronic	3%	82	20	22		****						
focal/multifocal vasculitis		-	m	~	<u></u>		• • •						
focal/multifocal/diffuse suppurative prostatitis	et ive	~	4	~	•								
	-	-	- :	- :	_	-			-	- :	-	_	

Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

(Study Locked)

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summary of eli Mistomorphologic findings

		:	:			COLUMN OF THE STATE OF THE STAT	MOTIVATION OF	CHUMER	<u> </u>		
:				MALES	ES		•		FEMALES	.fs	:
	TREATMENT	0 mg/kg	200 mg/kg	1000 mg/kg	1000 2000 mg/kg mg/kg		#0 #mg/kg	70 200 Pmg/kg mg/kg	1000 mg/kg	2000 mg/kg	
REPRODUCTIVE SYSTEM - MALE:-	•				:				:	:	:
PROSTATE:		(99)	(20)	(20)	(65)		* *			·	
Focal vascular mineralization				-			* *			- -	
Metastatic site: MESOTHELIONA (M)		-									
LYMPHOMA [M]		m	~	-	~						
focal epithelial hyperplasia			-				* *			-	
Multifocal interstitial fibrosis			-	-			-				
Focal/multifocal acinar ectasia		•	•	•	~	·					
Autolysia		-	~	-	~	 -	• •				
SEMINAL VESICLE(S):		(20)	(\$0)	(20)	(49)	<u> </u>					-
No abnormality detected		5	~	-	~	_	• •			· · ·	
Metastatic site: MISTIOCYTIC SARCOMA [M]	DHA [H]	-	~		_	-,					

22-FEB-96 75 PLACES VB.200

Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summery of all Mistomorphologic Findings

OBSERVATIONS TREATMENT REPRODUCTIVE SYSTEM - MALE:- SEMIMAL VESICLE(\$): Focal/multifocal/diffuse subscute/chronic inflammation	0 200 1000 2000 mg/kg mg/kg mg/kg (50) (50) (50) (49)	200 200 mg/kg (50)	Mg/kg mg/kg mg/kg 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 10000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 10000 22 10000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1000 22 1	2000 mg/kg mg/kg (49)		FEMALES 80 200 1000 2000 8mg/kg mg/kg mg/kg	FEMALES 1000 200 mg/kg mg	2000 mg/kg	
	0 mg/kg (50)	200 mg/kg (50)	1000 mg/kg (50)	2000 mg/kg (49)		200 mg/kg	1000 mg/kg	2000 mg/kg	
REPRODUCTIVE SYSTEM - MALE:- SEMINAL VESICLE(S): Focal/multifocal/diffuse subscute/chronic inflammation	(50)			§ 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5				:	
SEMINAL VESICLE(S): Focal/multifocal/diffuse subscute/chronic inflammation	(50)			(69)	 ***				
focal/multifocal/diffuse subscute/chronic inflammation	8	ū		2	 * 1				
				-					
Decreased secretory contents	-		-						
Focal/multifocal vasculitis			~		* *				
Diffuse/NOS acute/NOS seminal vesiculitis		-		-					
LYMPHOMA [M]	~	~	-	~					
Diletion	æ	88	43	17	 • •			-	
Autolysis	~	<u> </u>	•	m	• •			<u> </u>	
Abscess(es)	-		·			-	-		

Figures in brackets represent the number of animals from which this tissue was examined microscopically.
The absence of a numeral indicates that the lesion specified was not identified.

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7
Summery of all Mistomorphologic Findings

					INCID	INCIDENCE OF OBSERVATION (NUMERIC)	OBSERVA	NO CH	MERIC	_		
•				MALES	ES		*			FEMALES	ES	
OBSERVATIONS		o mg/kg	0 200 1000 2000 mg/kg mg/kg	1000 mg/kg	2000 mg/kg			70 200 70 200 70 mg/kg mg/	200 1000 mg/kg mg/kg	000 8/kg	2000 mg/kg	
REPRODUCTIVE SYSTEM - MALE:-	0 0 0 0 0 0 0		:			:		:	:	:		<u>:</u> <u>:</u>
TESTIS(ES):		(20)	(65)	§	(69)		•					
No abnormality detected		2	ŧ	%	2		* *			·		····
Metastatic site: HISTIOCYTIC SARCOMA [M]	RCOMA (M)		-		_		* *:					
Focal/multifocal interatitial/NOS acute/chronic inflammation	S	•	*1	-	м							
focal/multifocal vasculitis		~	8		~		* * :					
One examined			-	~			• •					
Focal sperm granulome(ta)		-			~	···-				·		
Multifocal/diffuse/NOS oligospermia	•	7	~	\$	-		• •					
Focal/multifocal mineralization		2	٥	~	*		• •					
Metastatic site: MESOTHELIONA (M)	=	-					• • •					
LYMPHOMA (M)		7	_		~		* *					

Figures in brackets represent the number of animals from which this tissue was examined microscopically.

The absence of a numeral indicates that the lesion specified was not identified.

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Oncogenicity Study (24-Nonths) of S-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summary of all Mistomorphologic Findings

,					INCIDEN	INCIDENCE OF OBSERVATION (NUMERIC)	SERVATION (NUMER	CHUMER				:-
•				MALES	: :		*		FEMALES	LES		:
OBSERVATIONS	TREATMENT	0 mg/kg mg/kg	200 mg/kg	1000 mg/kg	1000 2000 mg/kg mg/kg		#0 #mg/kg	200 mg/kg	#0 200 1000 2000 #mg/kg mg/kg mg/kg	2000 mg/kg		
REPRODUCTIVE SYSTEM - MALE:-						<u> </u>					<u>:</u>	:
TEST18(ES):		(20)	(65)	(69)	(6)		* *					
Focal/NOS INTERSTITIAL CELL ADENGHA	HOMA (B)	•			-	···.						
Multifocal tubular epithelial hyperplasia		_					* * *					·
Multifocal/diffuse interatitial cell hyperplasia	cell	m	~	-	4							
Multifocal interstitial fibrosis	•	-					* *					
focal capsular fibrosis				-			* *					
focal tubular dilation				-			* *					
focal/multifocal/diffuse seminiferous tubular degeneration	ferous	¥	31	2	90		* * *				· ·	
Multifocal vascular degeneration			-					•			-	
Autolysis			m	-	-							•
	_	-	_	_	_	_	_			_		

Figures in brackets represent the number of anim is from which this tissue was examined microscopically.
The absence of a numeral indicates that the lesion specified was not identified.

Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summery of all Mistemorphologic Findings

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OBSERVATIONS REPRODUCTIVE SYSTEM - MALE:- TESTIS(ES): Multifocal interstitial amyloidosia RESPIRATORY SYSTEM:- LUMG: No abnormality detected Metastatic site: MISTIOCYTIC SARCORA [M]					ENCE OF O	INCIDENCE OF OBSERVATION (NUMERIC)	((NUME	()		,	:
SERVATIONS DUCTIVE SYSTEM - MALE:- S(ES): Ltifocal interstitial amyloido RATORY SYSTEM:- abnormality detected abstatic site: MISTIOCYTIC SAR			MALES	:		•		FEMALES	165		
OUCTIVE SYSTEM - MALE:- S(ES): [tifocal interstitial amyloido RATORY SYSTEM:- abnormality detected testatic site: MISTIOCYTIC SAR	0 111	200	000	2000	-			:			:
REPRODUCTIVE SYSTEM - MALE:- IESTIS(ES): Multifocal interstitial amyloidosis RESPIRATORY SYSTEM:- LUNG: No abnormality detected Metastatic site: MISTIOCYTIC SARCORA (M		mg/kg mg/kg mg/kg	mg/kg	mg/kg		Fmg/kg	200 mg/kg	200 1000 2000 mg/kg mg/kg mg/kg	2000 mg/kg		
HESTIS(ES): Multifocal interatitial amylaidosis RESPIRATORY SYSTEM:- LUNG: No abnormality detected Hetastatic site: HISTIOCYTIC SARCORA [N				:	<u>:</u> :		:		:	:	
Multifocal interstitial amyloidosis RESPIRATORY SYSTEM:- LUNG: No abnormality detected Hetastatic site: HISTIOCYTIC SARCORA [N	(20)	(65)	(49)	(6)							
RESPIRATORY SYSTEM:- LUNG: No abnormality detected Hetastatic site: HISTIOCYTIC SARCONA [H	~		4	-		* *					
LUNG: No abrormality detected Hetastatic site: HISTIOCYTIC SARCONA [N				-		~ ~					
No abnormality detected Hetastatic site: HISTIOCYTIC SARCONA [H	(50)	(50)	(20)	(30)		(20)	(65)	(50)	(30)		
Metestatic site: HISTIOCYTIC SARCONA (N	2	5	Ξ	•••				12			
	-	m		_		√ • •	~	\$			
Metastatic site: GRANULOCYTIC LEUKENIA (M)		-		-		* * *					
Multifocal submucosal glandular acute inflammation	-					* * *					
Multifocal vasculitis	~	~	•	~		ر ا	7	4	-		
Metastatic site: BASOSGUAMOUS CARCINOMA (M)				· · · · · · · · · · · · · · · · · · ·			•		-		-

Figures in brackets represent the number of animals from which this tissue was examined microscopically
The absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Wonths) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summary of all Mistemorphologic findings

					I S	INCIDENCE OF OBSERVATION (NUMERIC)	OBSERVAT	101 E	JHERIC	_		
•				MALES	ES		•			FEMALES	ES	
OBSERVAT JONS	TREATMENT		0 200 1000 2000 mg/kg mg/kg mg/kg	1000 mg/kg	2000 mg/kg		2 . .	#0 200 1000 2000 #mg/kg mg/kg mg/kg	: <u>- </u>	000 9/kg	2000 mg/kg	
RESPIRATORY SYSTEM:-		:	:		1	:		:	:	:		<u> </u>
LUNG:		(20)	(30)	(20)	(30)		 	(20)	(65)	(20)	- G	
focal granulome(ta)					-		* * :		-			
focal bronchiolar mucous accumulation	lation						-				·	
Focal/multifocal vascular thrombosis	bosis			-	-	<u></u>	• •				-	
Multifocal pneumonia												
Multifocal/diffuse perivascular/alveolar edema			-	-	~		~			~		
Focal/multifocal vascular/NOS mineralization	_	-		~			***			4	m	
Primary site: NESOTHELIONA (N)				-								
LYMPHOMA (M)		•	7	-	~	-	•			•		

Figures in brackets represent the number of animals from which this tissue was examined microscopically.
The absence of a numeral indicates that the lesion specified was not identified

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Oncogenicity Study (24-Months) of 5-ASA in the Diet of Swiss Mice Project No. 862.09.00-CD Pathology Table 7 Summary of all Mistomorphologic findings

						ENCE OF 1	INCIDENCE OF OBSERVATION (NUMERIC)	DN (NUME	RIC)			:-
•				MALES	2		*	:	FEMALES	ILES		:
OBSERVATIONS	TREATMENT	0 mg/kg	0 mg/kg mg/kg	1000 mg/kg	1000 2000 mg/kg mg/kg		#0 #mg/k	200 g mg/kg	#0 200 1000 2000 #mg/kg mg/kg mg/kg mg/kg	2000 mg/kg		:
RESPIRATORY SYSTEM:-				:	:	:		:	:	:	:	:
LUNG:		(50)	(20)	(20)	(\$0)		(SO)	(49)	(20)	(\$0)	·	
Focat/multifocat pleurat/interstitial/bronchiola r/NOS acute/subacute/chronic/chronic- \$ inflammation	ronchioler/elveole /chronic-ective/NO	2	12	22	91		****	2	د	71		
focal/multifocal mesothelial hyperplasia		n					* * * :					
Focal tymphoid hyperplasia							-	<u></u> -				
focal epithelial hyperplasia							-					
focal/multifocal alveolar-cell hyperplasia		60	m	.	~		•	<u>~</u>	•	~		
focal/multifocal/diffuse alveolar histiocytosis	_	٠	•	21	2			•	•	~		<u> </u>
	`	•		•				•	-		•	- :

Figures in brackets represent the number of animals from which this tissue was examined microscopically. The absence of a numeral indicates that the lesion specified was not identified